

DESIGNER PEPTIDES: FROM MOLECULAR RECEPTORS TO SELF-ASSEMBLING SYSTEMS WITH EMERGENT PROPERTIES

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DESIGNER PEPTIDES: FROM MOLECULAR RECEPTORS TO SELF-ASSEMBLING SYSTEMS WITH EMERGENT PROPERTIES

by

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CERTIFICATE

This is to certify that the thesis entitled, "**Designer Peptides: from Molecular Receptors to Self-Assembling Systems with Emergent Properties**", being submitted by Mr. Rachit Sapra, to the Indian Institute of Technology Delhi, for the award of degree of Doctor of Philosophy in Chemistry, is a record of bonafide research work carried out by him. **Mr. Rachit Sapra** has worked under my guidance and supervision and has fulfilled all the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard. The results embodied in this thesis have not been submitted in part or in full, to any other University or Institute for award of any degree or diploma.



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ABSTRACT

The thesis titled "**Designer Peptides: from Molecular Receptors to Self-Assembling Systems with Emergent Properties**" showcases the development of novel characteristics resulting from peptide self-assembly. The distinct properties so generated can be used as a tool to explore self-assembly without the need for any external agent, as well as for an array of therapeutic and diagnostic applications. The thesis's work is organized into five chapters.

Chapter 1

The first chapter provides an overview of molecular recognition and self-assembly, as well as their role in disease causation, diagnosis, and treatment. The section also describes the most efficient and selective molecular receptors for recognizing C₆₀ fullerenes. The significance of peptides in designing self-assembling structures has also been addressed. Furthermore, the advent of new features induced by self-assembly and their application, with a focus on drug delivery, is highlighted.

Chapter 2

A series of oxidized cysteinyl peptides ([P-Cys-X-OMe]₂; P = Boc or H; X = Trp or Glu) showed vesicular and fibrillar assemblies. The anatomy of the self-assembled vesicles from the water-soluble cystine dipeptide, [Cys-Trp-OMe]₂ (**B2**) has been investigated by using various fluorescent probes such as ammonium 8-anilinonaphthalene-1-sulfonate, Nile Red and pyrene. The self-assembled structures are also observed in solution as evident from the quantitative phase images obtained using a dual-mode digital holographic microscope (DHM) system. Present investigations show that the self-assembly is enthalpy- and entropy-driven in the aqueous

medium. Based on the CD spectral studies, we proposed that **B2** organize into vesicles through sequestration of indole units. We also found that the vesicles formed by **B2** can act as a host for guests like C₆₀. The biocompatibility and biodegradability of these peptides along with the autofluorescent nature and guest binding ability of peptide-based vesicles offer numerous applications in the biomedical area.

Chapter 3

We observed that the solutions of cysteinyl peptides **B1** and **B2** exhibit intense autofluorescence in the blue region upon excitation at wavelength >350 nm. Detailed spectroscopic studies on the peptides lacking tryptophan **C1** and **C2** unequivocally showed that the autofluorescence stems exclusively from peptide aggregation. Our experimental results with appropriate controls revealed that clustering of carbonyl chromophores is central to the autofluorescence. Autofluorescence was also used to probe the vesicle formation without using any external fluorescent probe. To the best of our knowledge, this is the first example of autofluorescent vesicles formed by the spontaneous association of dipeptides. The biocompatibility and biodegradability of these peptides along with the autofluorescent nature and guest (C₆₀) binding ability of peptide-based vesicles offer numerous applications in the biomedical area.

Chapter 4

In this chapter, we employed a chemical reduction approach to synthesize amino acid- and peptide-capped gold nanoparticles and assessed their ability to detect various antibiotic classes. The studies revealed that Boc-cystine-capped nanoparticles allow selective detection of fluoroquinolones ciprofloxacin and norfloxacin in water with detection limits 65 and 92 nM, respectively. Antibiotics added to nanoparticles caused them

to aggregate, indicated by a change in color from wine red to purplish blue and spectral changes. The interactions that underpin nanoparticle binding to ciprofloxacin and norfloxacin were also examined.

Chapter 5

A series of ferrocene-amino acid conjugates were synthesized and investigated for their cation binding affinity using UV-vis and fluorescence spectroscopy, and cyclic voltammetry. Tryptophan-containing ferrocenoyl receptors **E3** and **E7** showed selective Fe^{3+} and Cu^{2+} binding ability with detection limits in the low micromolar range. The presence of Fe^{3+} and Cu^{2+} was also indicated by colorimetric response that facilitates their onsite detection without the use of sophisticated instruments. Along with the color transitions, the metal complexation by the receptors was monitored by UV-vis and electrochemical measurements and the tentative binding modes have been proposed. The series of changes observed in spectroscopic studies were supported by cyclic voltammetric experiments. The formation of metal-ion complex was also supported by fluorescence emission spectroscopy. The detailed UV-vis spectroscopic studies on ferrocenoyl receptors lacking tryptophan **E4** and **E8** revealed the crucial role played by tryptophan in metal binding *via* cation- π interactions. The effect of addition of Fe^{3+} and Cu^{2+} ions on the morphology of these receptors was also studied using scanning and transmission electron microscopy.

सारांश

"डिजाइनर पेप्टाइड्स: आणविक रिसेप्टर्स से लेकर एमर्जेंट प्रॉपर्टीज के साथ सेल्फ-असेंबलिंग सिस्टम" नामक थीसिस पेप्टाइड सेल्फ-असेंबली से उत्पन्न नई विशेषताओं के विकास को दर्शाती है। इस प्रकार उत्पन्न विशिष्ट गुणों का उपयोग किसी भी बाहरी एजेंट की आवश्यकता के बिना स्व-असेंबली का पता लगाने के लिए एक उपकरण के रूप में किया जा सकता है, साथ ही चिकित्सीय और नैदानिक अनुप्रयोगों की एक सरणी के लिए भी। थीसिस का काम पांच अध्यायों में आयोजित किया गया है।

Chapter 1

पहला अध्याय आणविक मान्यता और आत्म-संयोजन का अवलोकन प्रदान करता है, साथ ही रोग के कारण और उपचार में उनकी भूमिका भी प्रदान करता है। अनुभाग C₆₀ फुलरीन को पहचानने के लिए सबसे कुशल और चयनात्मक आणविक मान्यता विधि का भी वर्णन करता है। स्व-संयोजन संरचनाओं को डिजाइन करने में पेप्टाइड्स के महत्व को भी संबोधित किया गया है। इसके अलावा, दवा वितरण पर ध्यान देने के साथ स्व-विधानसभा और उनके आवेदन से प्रेरित नई सुविधाओं के आगमन पर प्रकाश डाला गया है।

Chapter 2

ऑक्सीकृत साइस्टीनिल पेप्टाइड्स की एक श्रृंखला ([P-Cys-X-OMe]₂; P = Boc or H; X = Trp or Glu) ने वेसिकुलर और फाइब्रिलर असेंबली दिखाई। पानी में घुलनशील सिस्टीन डाइपेप्टाइड, [Cys-Trp-OMe]₂ (B2) से स्व-इकट्टे पुटिकाओं की शारीरिक रचना की जांच अमोनियम 8-एनिलिनोनेफ्थलीन -1-सल्फोनेट, नाइल रेड और पाइरीन जैसे विभिन्न फ्लोरोसेंट जांच का उपयोग करके की गई है। स्व-इकट्टी संरचनाओं को समाधान में भी देखा जाता है जैसा कि दोहरे-मोड डिजिटल होलोग्राफिक माइक्रोस्कोप (डीएचएम)

प्रणाली का उपयोग करके प्राप्त मात्रात्मक चरण छवियों से स्पष्ट है। वर्तमान जांच से पता चलता है कि जलीय माध्यम में स्व-सभा एन्थैल्पी- और एन्ट्रॉपी-संचालित है। सीडी स्पेक्ट्रल अध्ययनों के आधार पर, हमने प्रस्तावित किया कि **B2** इंडोल इकाइयों के अनुक्रम के माध्यम से पुटिकाओं में व्यवस्थित ऑटोफ्लोरोसेंट प्रकृति और पेप्टाइड-आधारित पुटिकाओं की अतिथि बाध्यकारी क्षमता के साथ इन पेप्टाइड्स की जैव-रासायनिकता और बायोडिग्रेडेबिलिटी बायोमेडिकल क्षेत्र में कई अनुप्रयोग प्रदान करती है। होता है। हमने यह भी पाया कि **B2** द्वारा गठित पुटिकाएं C_{60} जैसे मेहमानों के लिए एक मेजबान के रूप में कार्य कर सकती हैं।

Chapter 3

हमने देखा कि साइस्टीनिल पेप्टाइड्स **B1** और **B2** के समाधान तरंग दैर्ध्य >350 nm पर उत्तेजना पर नीले क्षेत्र में तीव्र ऑटोफ्लोरोसेंस प्रदर्शित करते हैं। ट्रिप्टोफैन **C1** और **C2** की कमी वाले पेप्टाइड्स पर विस्तृत स्पेक्ट्रोस्कोपिक अध्ययन ने स्पष्ट रूप से दिखाया कि ऑटोफ्लोरोसेंस विशेष रूप से पेप्टाइड एकत्रीकरण से उपजा है। उचित नियंत्रण के साथ हमारे प्रयोगात्मक परिणामों से पता चला है कि कार्बोनिल क्रोमोफोर का क्लस्टरिंग ऑटोफ्लोरोसेंस के लिए केंद्रीय है। किसी भी बाहरी फ्लोरोसेंट जांच का उपयोग किए बिना पुटिका गठन की जांच के लिए ऑटोफ्लोरोसेंस का भी उपयोग किया गया था। हमारे ज्ञान के अनुसार, यह डाइपेप्टाइड्स के सहज संघ द्वारा गठित ऑटोफ्लोरोसेंट पुटिकाओं का पहला उदाहरण है। पेप्टाइड-आधारित पुटिकाओं की ऑटोफ्लोरोसेंट प्रकृति और अतिथि (C_{60}) बाध्यकारी क्षमता के साथ इन पेप्टाइड्स की जैव-रासायनिकता और बायोडिग्रेडेबिलिटी बायोमेडिकल क्षेत्र में कई अनुप्रयोग प्रदान करती है।

Chapter 4

इस अध्याय में, हमने अमीनो एसिड- और पेप्टाइड-कैप्ड गोल्ड नैनोकणों को संश्लेषित करने के लिए

रासायनिक कमी दृष्टिकोण को नियोजित किया और विभिन्न एंटीबायोटिक वर्गों का पता लगाने की उनकी क्षमता का आकलन किया। अध्ययनों से पता चला है कि Boc-cystine-कैप्ड नैनोपार्टिकल्स क्रमशः 65 और 92 nM की पहचान सीमा के साथ पानी में फ्लोरोक्विनोलोन, सिप्रोफ्लोक्सासिन और नॉरफ्लॉक्सासिन का चयनात्मक पता लगाने की अनुमति देते हैं। नैनोकणों में जोड़े गए एंटीबायोटिकदवाओं ने उन्हें वाइन लाल से बैंगनी नीले और वर्णक्रमीय परिवर्तनों में रंग में बदलाव से संकेत दिया। सिप्रोफ्लोक्सासिन और नॉरफ्लॉक्सासिन के लिए नैनोपार्टिकल बाइंडिंग को रेखांकित करने वाले इंटरैक्शन की भी जांच की गई।

Chapter 5

फेरोसीन-अमीनो एसिड संयुग्मों की एक श्रृंखला को यूवी-विस और फ्लोरोसेंस स्पेक्ट्रोस्कोपी, और चक्रीय वोल्तामेट्री का उपयोग करके उनके केशन बाइंडिंग संबंध के लिए संश्लेषित और जांच की गई थी। ट्रिफ्लैकैन युक्त फेरोसेनोयल रिसेप्टर्स E3 और E7 ने कम माइक्रोमोलर रेंज में पहचान सीमा के साथ चयनात्मक Fe^{3+} और Cu^{2+} बाइंडिंग क्षमता दिखाई। Fe^{3+} और Cu^{2+} की उपस्थिति को कलरिमेट्रिक प्रतिक्रिया द्वारा भी इंगित किया गया था जो परिष्कृत उपकरणों के उपयोग के बिना उनकी ऑनसाइट पहचान की सुविधा प्रदान करता है। रंग संक्रमण के साथ, रिसेप्टर्स द्वारा धातु परिसर की निगरानी यूवी-विस और इलेक्ट्रोकेमिकल माप द्वारा की गई थी और अस्थायी बाध्यकारी मोड प्रस्तावित किए गए हैं। स्पेक्ट्रोस्कोपिक अध्ययनों में देखे गए परिवर्तनों की श्रृंखला चक्रीय वोल्तामेट्रिक प्रयोगों द्वारा समर्थित थी। धातु-आयन परिसर के गठन को प्रतिदीप्ति उत्सर्जन स्पेक्ट्रोस्कोपी द्वारा भी समर्थित किया गया था। ट्रिफ्लैकैन E4 और E8 की कमी वाले फेरोसेनोयल रिसेप्टर्स पर विस्तृत यूवी-विस स्पेक्ट्रोस्कोपिक अध्ययन ने केशन- π इंटरैक्शन के माध्यम से धातु बंधन में ट्रिफ्लैकैन द्वारा निभाई गई महत्वपूर्ण भूमिका का खुलासा किया। स्कैनिंग और ट्रांसमिशन इलेक्ट्रॉन माइक्रोस्कोपी का उपयोग करके इन रिसेप्टर्स की आकृति विज्ञान पर Fe^{3+} और Cu^{2+} आयनों के अतिरिक्त प्रभाव का भी अध्ययन किया गया था।

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LIST OF ABBREVIATIONS

^{13}C NMR	^{13}C Nuclear Magnetic Resonance
^1H NMR	^1H Nuclear Magnetic Resonance
ΔH_{assoc}	Enthalpy Change on Association
ΔS_{assoc}	Entropy Change on Association
λ_{ex}	Excitation Wavelength
λ_{em}	Emission Wavelength
λ_{max}	Maximum Wavelength
ΔG_{assoc}	Gibb's Free Change on Association
μg	Micro gram
μL	Micro Litre
μm	Micro meter
μM	Micro molar
AgNPs	Silver Nanoparticles
AIE	Aggregation Induced Emission
AuNPs	Gold Nanoparticles
AZM	Azithromycin
Boc	Bis-tert-butyloxycarbonyl
C_{60}	Buckminster Fullerene
CAC	Critical Aggregation Concentration
CD	Circular Dichroism
CH_3CN	Acetonitrile

$(\text{COCl})_2$	Oxalyl Chloride
CIP	Ciprofloxacin
CHCl_3	Chloroform
CLM	Clarithromycin
$\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	Copper(II) Chlorate hexahydrate
$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$	Copper(II) Sulfate pentahydrate
CV	Cyclic Voltammetry
DCC	Dicyclohexylcarbodiimide
DHM	Digital Holographic Microscope
DLS	Dynamic Light Scattering
DPV	Differential Pulse Voltammetry
ΔE	Difference Half-Wave Potentials
EDX	Energy Dispersive X-Ray
E_{pa}	Anodic Half-Wave Potentials
E_{pc}	Cathodic Half-Wave Potentials
E_{redox}	One-electron Redox Potentials
exTTF	Extended Tetrathiafulvalene
Fc	Ferrocene
Fc^+	Ferrocenium
$\text{Fe}(\text{ClO}_4)_3 \cdot 6\text{H}_2\text{O}$	Iron(III) Chlorate hexahydrate
FLIM	Fluorescence Lifetime Imaging
$\text{HAuCl}_4 \cdot 3\text{H}_2\text{O}$	Hydrogen Tetrachloroaurate(III) trihydrate

HPLC	High-performance liquid chromatography
I_{ac}	Maximum Anodic Peak Current
I_{pc}	Maximum Cathodic Peak Current
IR	Infrared
IRF	Instrument Response Function
ITC	Isothermal Titration Calorimetry
$K_2Cr_2O_7$	Potassium Dichromate
K_a	Association Constant
K_{SV}	Stern-Volmer Constant
KOH	Potassium Hydroxide
LOD	Limit of Detection
LOQ	Limit of Quantification
MLCT	Metal to Ligand Charge Transfer Interactions
mM	Milli molar
mV	Milli volt
$NaBH_4$	Sodium Borohydride
NaOH	Sodium hydroxide
Na_2SO_4	Sodium Sulfate
NEt_3	Triethylamine
NFX	Norfloxacin
NHS	N-Hydroxysuccinimide
nm	Nano meter

nM	Nano molar
NPs	Nanoparticles
NR	Nile Red
ppm	Parts Per Million
rpm	Rounds Per Minute
REES	Red Edge Excitation Shift
RXM	Roxithromycin
<i>S. aureus</i>	<i>Staphylococcus aureus</i>
SDDDS	Supramolecular Drug-Drug Delivery System
SEM	Scanning Electron Microscope
<i>S. pneumoniae</i>	<i>Streptococcus pneumoniae</i>
SPR	Surface Plasmon Resonance
SR-SIM	Super Resolution-Structured Illumination Microscopy
SrtA	Sortase A
SZS	Sulphonamide
TCY	Tetracycline
TBAP	Tetra-n-butylammonium perchlorate
TCSPC	Time-Correlated Single Photon Counting
TEM	Transmission Electron Microscope
TFA	Trifluoroacetic Acid
Trp	Tryptophan

TTF

Tetrathiafulvalene

UV-vis

UV-Visible

NOTES

1. All amino acids utilized in the syntheses were of L-configuration and were purchased from SRL India. Unless otherwise specified, amino acids are represented using the conventional single/triple letter codes.
2. Unless otherwise noted, all commercial chemicals and reagents used in chemical syntheses were acquired from Sigma-Aldrich or Alfa Aesar and used as received with no further purification.
3. Prior to use, all solvents used in the processes were distilled/dried according to established methods.
4. All air sensitive reactions were performed in oven dried glassware in an inert environment of argon or nitrogen.
5. Wherever possible, all reactions were monitored using silica gel thin layer chromatography (TLC).
6. To purify all the produced compounds, we used silica gel column chromatography with a mesh size of 100-200. The slurry was generally made in chloroform, DCM and/or MeOH.
7. ^1H NMR, ^{13}C NMR, IR, and High Resolution Mass Spectrometry (HRMS) were used to characterize the synthesized compounds.
8. The Bruker-DPX-300/400/500 MHz spectrometer was used to obtain ^1H NMR, ^{13}C NMR spectra, with chemical shifts relative to tetramethylsilane (TMS) reported downfield. ^1H -NMR data are reported as br (broad), s (singlet), d (doublet), q (quartet), t (triplet) and m (multiplet). ^1H NMR coupling constants are reported in Hz.

9. Using the Electrospray Ionization (ESI) technique, high resolution mass spectra (HRMS) were recorded in the Bruker MicrO-TOF-QII model.
10. IR spectra were recorded on Agilent-Cary 660 Series FTIR spectrometer/Nicolet, Protégé 460 spectrometer as KBr Pellets.
11. Melting points were measured using a Fisher-Scientific melting point instrument.